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BP CHEMICALS

BP Chemicals Inc.
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Cleveland, Ohio 44114-2375
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OFFICE OF POLLUTION PREVENTION AND TOXICS
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U.S. Environmental Protection Agency
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Washington, DC 20460

8EHQ-92-12836
8892001090 1

Attn: TSCA Section 8(e) Coordinator (CAP Agreement)

Re: EPA ID No. 8ECAP-0009

Dear Sir or Madam:

BP Chemicals, Inc. submits the attached study pursuant to the terms of the TSCA Section 8(e) Compliance Audit Program (CAP) and the BP America CAP Agreement:

Study Identification

Toxicity Studies with HEMA (Hydroxyethyl Methacrylate) and Related Studies; Report No. 25-90-0044 dated March 10, 1981.

HEMA was evaluated in the following biological assays:

Skin Irritancy in Rabbits
Skin Sensitization in Guinea Pigs
Eye Irritancy in Rabbits
Mutagenicity in Salmonella typhimurium

HPMA (Hydroxypropyl Methacrylate), HPA (Hydroxypropyl Acrylate), and HEA (Hydroxyethyl Acrylate) were also evaluated in the skin irritancy assay. MA (Methacrylic Acid) was also evaluated in the skin sensitization assay.

Identity of Tested Chemical Substance/Mixture and CAS Number (if known)

Hydroxyethyl Methacrylate (CAS No. 868-77-9); Hydroxypropyl Methacrylate (CAS No. 923-26-2); Hydroxypropyl Acrylate (CAS No. 999-61-1); Hydroxyethyl Acrylate (CAS No. 818-61-1); and Methacrylic Acid (CAS No. 79-41-4).

Summary of Results

Skin Irritancy in Rabbits

HEMA and HPMA were found to be mildly irritating to rabbit skin. HPA and HEA were found to be severe irritants producing necrosis, subcutaneous

hemorrhage and pitting edema over a wide area of skin. The reaction was particularly severe in the case of HEA.

Skin Sensitization in Guinea Pigs

HEMA was shown to be a potent contact sensitizer in the guinea pig maximization assay. Results do not support the theory that free MA content of HEMA is responsible for HEMA's sensitizing potential, although results indicate cross reactivity with MA. This suggests that individuals sensitized to HEMA may also react to MA.

Eye Irritation in Rabbits

HEMA was severely irritating to the rabbit eye.

Bacterial Mutagenicity

HEMA was not mutagenic to bacteria in the Ames assay.

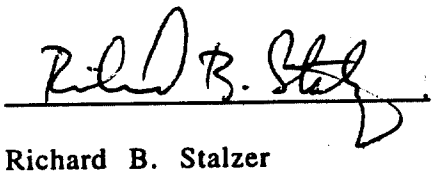
The results of this program are consistent with the known toxic effects of low molecular weight acrylates and methacrylates.

Previous PMN or 8(e) Submissions by BPA: EPA Document Control Number(s)

None.

BP Chemicals imports HEMA, HPMA, HPA and HEA into the U.S. Warnings about the hazards defined in this program are included on product labels and Material Safety Data Sheets for these chemicals.

Submitted by:



Richard B. Stalzer
Manager, Health, Safety and
Environmental Quality
BP Chemicals, Inc.
216-586-5311

August 25, 1992

Date

6 2 1

TOXICOLOGY REPORT
25-90-0044

TOXICITY STUDIES WITH HEMA AND RELATED SUBSTANCES PART I

BP
GROUP OCCUPATIONAL HEALTH CENTRE
British Petroleum Company Ltd. Chertsey Road, Sunbury-on-Thames, Middlesex TW16 7LN
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GROUP OCCUPATIONAL HEALTH CENTRE

TOXICOLOGY REPORT
25-90-0044

TOXICITY STUDIES WITH HEMA AND RELATED SUBSTANCES PART I

WRITTEN BY: DR. F.M.B. CARPANINI

APPROVED BY: DR. M. SHARRATT

ISSUED: 10 MARCH 1981

Distribution

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7	Author
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CONTENTS

SUMMARY

Studies were carried out of the mutagenic potential and eye irritancy of hydroxyethyl methacrylate (HEMA), the cutaneous sensitising potential of HEMA and methacrylic acid (MA) and the skin irritancy of HEMA, two competitor samples (HEMA I and HEMA II), hydroxypropyl methacrylate (HPMA), hydroxyethyl acrylate (HEA) and hydroxypropyl acrylate (HPA).

The results indicate that HEMA is a potent contact sensitiser, a property which appears to be independent of the residual methacrylic acid levels. The monomer is also irritant to the skin and eye producing corneal damage and tissue inflammation in rabbits. Washing the eyes immediately with water following accidental contamination is likely to reduce the severity and duration of the reaction. There was no evidence of mutagenic activity on the part of HEMA as shown in the 'Ames' tests.

On the basis of the result of the guinea-pig sensitisation studies and the skin irritancy studies in rabbits, it was not possible to distinguish between HEMA, HEMA I and HEMA II.

Tests in guinea pigs failed to demonstrate any sensitising potential with MA.

Both HPA and HEA produced severe skin damage in rabbits following exposure under occlusion; skin and eye contact with these materials should be avoided.

1. INTRODUCTION

Following the development of a purer grade of hydroxyethyl methacrylate (HEMA), BPCL requested advice from GOHC on the safe handling of the new product. The studies summarised here form part of a programme of toxicological studies designed to provide sufficient information to satisfy the requirements of the Health and Safety at Work Act, 1974, and as a basis for providing sound advice on safe-handling.

Other grades of HEMA have been associated with high incidences of allergic skin sensitisation in workers employed in the printing industry and it has been suggested that these reactions are due to the free methacrylic acid content of the product. In order to test this hypothesis, the sensitisation study compared the allergenic potential of the BPCL grade of HEMA with that of methacrylic acid (MA) and provided for cross-challenge of the MA-sensitised animals with hydroxypropyl methacrylate (HPMA) and competitor grades of HEMA.

In addition, GOHC were asked by BPCL to compare the primary skin irritancy of HPMA, HEMA and hydroxypropyl acrylate (HPA) (ex BPCL) with those of the two grades of HEMA produced by another company and one sample of hydroxyethyl acrylate (HEA). (See memo ref. RAR/AAP, 23rd September 1980).

2. TEST MATERIALS

Samples of the following products were supplied by BPCL, Carshalton:

2.1 HEMA (BPCL Product).

2.2 HEMA I (Rohm Product).

2.3 HEMA II (Rohm & Haas Product).

2.4 MA

2.5 HPA (BPCL Product).

2.6 HEA (Competitor Product).

2.7 HPMA (BPCL Product).

3. INVESTIGATIONS

3.1 Primary Skin Irritation

The primary skin irritancy of HEMA, HEMA I, HEMA II, HPMA, HEA and HPA were assessed using albino rabbits.

The test materials were applied in 0.25 ml aliquots to areas of abraded and non-abraded shaved dorsal skin

and the sites covered for 24 hours with occlusive dressing. After removal of these patches any remaining test material was washed off with water and the reactions evaluated using the "Draize" scoring system approximately 1 (24 hr reading) and 48 hrs (72 hr reading) later.

The degrees of irritation observed with the products are summarised in Table 1 as Draize Scores. With the exception of HPA and HEA the degree of irritation produced by the materials was similar, all are likely to be mild irritants if contact with human skin occurs. HPA and HEA were found to be severe irritants producing necrosis, subcutaneous haemorrhage and pitting oedema over a wide area of skin. The reaction was particularly severe in the case of HEA. Histological examination of one area of skin exposed to HPA revealed epidermal necrosis together with areas of damage and haemorrhage extending deeply into the deep dermis and hypodermis.

3.2 Skin Sensitisation Studies

The sensitisation potentials of HEMA and MA were studied by the method of Magnusson and Kligman, 1969. Two weeks after topical induction, the animals were challenged for the first time. Test and control groups were challenged with 25% and 10% concentrations of HEMA. Additionally, the MA test and control groups were challenged with 5% and 2.5% solutions of MA.

One week after the first challenge, the test and control HEMA groups were challenged with 5% HEMA, 5% HEMA I and 5% HEMA II, 10% MA and 5% MA. Test and control MA groups were challenged with 10% and 5% MA. Skin reactions were evaluated at 48 and 72 hours following application of the challenge and re-challenge patches. Animals induced with HEMA were demonstrated to be sensitised; all reacted positively to a challenge with a 10% solution. Following the challenge with 5% solutions of HEMA, HEMA I and HEMA II, four of the sensitised animals responded to all three and a further two animals only to HEMA I and HEMA II. Eight of the animals also reacted to challenge with 10% MA. However, at this concentration there was some evidence of irritancy in the control animals so that the reaction may not have been wholly allergic in nature. The results show that HEMA is an extremely potent sensitiser and the two competitor samples, HEMA I and HEMA II, are similarly active. In addition, there is an indication of some cross-reactivity with MA.

The results of the studies revealed no evidence that the animals became sensitised to MA, the incidence of skin reactions being greater in the control than in the test group.

It may be concluded that all the grades of HEMA tested are potent sensitisers and could be expected to produce allergic contact sensitivity in some individuals following repeated exposure. The experimental results do not permit a comparison of the relative sensitising potentials of the three grades of HEMA. In addition, the results do not support the theory that the free MA content of HEMA is responsible for its sensitising potential though individuals sensitised to HEMA might well cross-react when exposed to MA.

3.3 Eye Irritation Studies

The eye irritancy of HEMA was assessed on albino rabbits; approximately 0.1 ml of neat HEMA was introduced into one eye of each animal. The ocular irritation produced by the material was assessed at approx. 3 hours, 1,2,3,7 and 15 days after instillation. Effects on the cornea were studied further using sodium fluorescein to confirm the presence of epithelial damage and a slit lamp to measure corneal thickness.

The animals reacted immediately to the instillation of the test material, the eyes remaining closed for a time. The numerical scores awarded to the ocular reactions are summarised in Table 2.

Instillation into the eye of HEMA resulted in immediate discomfort. The adverse effects on the conjunctivae and the cornea were long lasting. Fluorescein staining revealed large areas of corneal ulceration. There was, in addition, a definite increase in corneal thickness in all test animals, an effect which persisted for at least 7 days. In view of the continuing severity of the lesions at 7 days, observations were made at 15 days. These revealed that the rabbit eyes were almost back to normal although a minor corneal defect persisted in one animal.

It may be concluded that HEMA is severely irritant to the eye and may cause permanent injury, particularly if the material is not washed from the eye quickly. The studies did not include observations on the effect of washing the eyes following instillation of the test material although bearing in mind the solubility of HEMA it is likely that washing with water would significantly reduce the extent of damage.

3.4 Mutagenicity Studies

A sample of HEMA was tested with and without metabolic activation in S. typhimurium strains TA 98 and TA 100 and in E. coli strains R^{+}WP2 and uvrA and WP2. An occasional increase in the number of revertants over the control level was observed with TA 100 in the activated tests. However, this increase was not consistent or dose-related. Negative findings were obtained in fluctuation tests using TA 98 and TA 100, both with and without metabolic activation. The concentration range used in these studies was 0.2 to 1000 µg/ml. These results show that the material was not mutagenic in these systems.

4. DISCUSSION

4.1 HEMA

The studies have demomstrated that hydroxyethyl methacrylate irritates tissues with which it comes into contact. Although the skin irritancy in rabbits was mild, contact with eyes produced corneal damage and tissue inflammation which persisted for nearly 2 weeks. In addition, HEMA is a potent contact sensitiser, a property which appears to be largely independent of the residual methacrylic acid levels. Acute skin contact with HEMA is unlikely to produce severe reactions in man although repeated exposure could result in allergic or irritant dermatitis. There was no evidence of mutagenic activity in the 'Ames' tests conducted with HEMA, indicating that the monomer does not interact significantly with DNA. Its lack of activity in these tests supports the general impression gained from its structure, biological activity of related materials and the likelihood of its rapid metabolism to ethylene glycol and methacrylic acid, that HEMA is unlikely to present a carcinogenic hazard. Acute toxicity studies via the oral and percutaneous routes of administration have also been conducted with HEMA and the results will form part of a supplementary report.

4.2 HEMA I & HEMA II

The skin irritancy of these competitor products was assessed and compared with those of HEMA and HPMA. All were found to be mildly irritant and no significant differences in the response were observed. Cross-challenge of HEMA-sensitised guinea-pigs with HEMA I and HEMA II gave a response no greater than that of HEMA itself. On the basis of these results it is not possible to differentiate between HEMA, HEMA I and HEMA II in terms of their effects following skin contact.

4.3 HPA and HEA

Both of these materials produced severe skin damage following exposure under occlusion. Both can be classed as severely irritant; the extensive damage to both the epidermis and deep dermis suggest that the monomers are extensively absorbed through the skin. It follows that skin and eye contact with these materials should be avoided. Since HPA is a new BPCL product, early consideration should be given to reviewing the available toxicological data with a view to ensuring sufficient information exists to provide adequate advice on handling within the terms of HSE requirements.

4.4 MA

The theory that residual methacrylic acid levels in HEMA may be wholly or partly responsible for its sensitising properties was evaluated in the guinea-pig. The results provided no support for the theory but confirm the lack of sensitisation potential by MA observed when individuals sensitised to methyl methacrylate were challenged with methacrylic acid and a number of its esters. Positive reactions were obtained for all but MA.(6)

DR. F.M.B. CARPANINI

FMBC/CS
25.3.81

TABLE I

[redacted] SKIN IRRITATION STUDIES: TOTAL NUMERICAL SCORES AND CALCULATED MEAN IRRITATION INDICES

[redacted]ound	No. of Animals	Total Scores		Mean Irritation Index
		Erythema	Oedema	Erythema + Oedema
[redacted]	6	9.5	0	0.4
[redacted]	6	27.5	2.0	1.2
[redacted]	5†	13.0	0	0.7
[redacted] I	6	27.0	1	1.2
[redacted] II	6	21.5	0	0.9
[redacted]	4†	16.5	0	1.0
[redacted]	6	96	96	8.0
[redacted]	6	96	33	5.4

† "Unreadable" animal(s) excluded.

NUMERICAL SCORES OF OCULAR REACTIONS TO HEMA

[illegible]	Area of Eye	Score at Time					
		3 hr	1 day	2 days	3 days	7 days	15 days
AS1	Cornea	1	1	1	2	<1	0
	Iris	0	0	0	1	0	0
	Conjunct R.	2	2	2	3	1	0
	Conjunct C	2-3	2-3	2-3	4	1-2	0
	Conjunct D	3	3	3	3	0	1
AS2	Cornea	1	1-2	1-2	1-2	1	0
	Iris	0	0	0	0-1	0	0
	Conjunct R	2-3	2	1-2	1-2	1	0
	Conjunct C	2-3	2	1	1	1	0
	Conjunct D	3	3	0	1	0	0
AS3	Cornea	1	1	1	1-2	2	1
	Iris	0	0	0	0-1	0	0
	Conjunct R	2-3	1-2	2	2.3	<1	0
	Conjunct C	3-4	1-2	1-2	3-4	1	1
	Conjunct D	3	3	2	3	0	0

R = Redness

C = Chemosis

D = Discharge

REFERENCES

1. A Study of the Skin Irritancies of 2-hydroxyethyl-methacrylate (HEMA) (Various grades), 2-hydroxypropyl-methacrylate (HPMA) and hydroxyethyl acrylate (HEA) GOHC Experiment No. 8OT26 (A) & (B)

2. A Study of the Skin Sensitisation Potentials of 2-Hydroxyethyl Methacrylate (HEMA) and Methacrylic Acid (MA). GOHC Experiment No. 8OT27

3. A Study of the Eye Irritancy of 2-Hydroxyethyl Methacrylate (HEMA) GOHC Experiment No. 8OT28

4. A Study of the Skin Irritancies of 2-Hydroxyethyl Methacrylate (HEMA) and Hydroxypropylacrylate (HPA) GOHC Experiment No. 8OT30.

5. Regnier, A.P. Reports on 'Ames' Plate Tests with Hydroxyethyl Methacrylate 10.11.80.

(The above results are held in the GOHC Experimental archives/GOHC Information Services and are available on request).

6. Fisher, A.A., "Cross reactions between methyl methacrylate monomer and acrylic monomers presently used in acrylic nail preparations". Contact Dermatitis, 1980 6, 345.

Triage of 8(e) Submissions

Date sent to triage: _____ NON-CAP (CAP)

Submission number: 12836A TSCA Inventory: (Y) N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

(ATOX) SBTOX (SEN) w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX (GTOX)

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

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entire document: 0 (1) 2 **pages** 1 **pages** _____

Notes:

Contractor reviewer : JW **Date:** 11/24/96

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CECATS DATA:
Submission # 8EHQ- 0892-12836 SEQ. A

TYPE: (INT.) SUPP FLWP

SUBMITTER NAME: BP Chemicals Inc.

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER ROUTES
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 08/23/92 OTS DATE: 08/28/92 CSRAD DATE: 09/30/95

CHEMICAL NAME:

CAS#
868-77-9
923-26-9
25584-83-2 ~~999-61-1~~
818-61-1
per casonline

79-41-4

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
(0204)	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
(0212)	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
(0224)	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
(0228)	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

[redacted]

TRIAGE DATA:

NON-CBI INVENTORY
(YES)
NO
DETERMINE

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER:

SPECIES
RBT
GP
In Vitro

TOXICOLOGICAL CONCERN:
(LOW)
(MED)
(HIGH)

USE:

PRODUCTION:

CAS SR

COMMENTS:

12836A

L

HEMA: Dermal irritation in rabbits is of low concern. Application of 0.25 mL to the intact and abraded skin of six rabbits resulted in mild irritation.

L

HPMA: Dermal irritation in rabbits is of low concern. Application of 0.25 mL to the intact and abraded skin of six rabbits resulted in mild irritation.

H

HEA: Dermal irritation in rabbits is of high concern. Application of 0.25 mL to the intact and abraded skin of six rabbits resulted in severe irritation. Necrosis, subcutaneous hemorrhage, and pitting edema also occurred. Histological examination revealed damage extending into the deep dermis and hypodermis.

H

HPA: Dermal irritation in rabbits is of high concern. Application of 0.25 mL to the intact and abraded skin of six rabbits resulted in severe irritation. Necrosis, subcutaneous hemorrhage, and pitting edema also occurred.

H

HEMA: Dermal sensitization in guinea pigs is of high concern. A dermal sensitization test was conducted with guinea pigs (number of animals not provided) according to the Magnusson Kligman method. No results were provided for the first challenge with 25% and 10% solutions. Subsequent challenges elicited the following responses: all animals sensitized with a 10% solution; six animals sensitized with a 5% solution; and eight animals sensitized with a 10% solution of MA. The compound was classified as an extremely potent sensitizer.

L

MA: Dermal sensitization in guinea pigs is of low concern. A dermal sensitization test was conducted with guinea pigs according to the Magnusson Kligman method. No exhibited a positive response upon challenge.

M

HEMA: Eye irritation in rabbits is of moderate concern. Instillation of 0.1 mL of the substance into one eye of three rabbits resulted in severe irritation. Fluorescein staining revealed large areas of corneal ulceration. Increased corneal thickness also occurred, which persisted for at least 7 days. Observation at 15 days revealed that most of the irritation subsided; only a "minor corneal defect" was observed (1/3 rabbits).